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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
03/18/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/542,238	FRESON ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-32* is/are pending in the application.

4a) Of the above claim(s) *16-20,22,25,26,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15,21,24 and 27-29* is/are rejected.

7)☒ Claim(s) *23 and 32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received January 9, 2009 are acknowledged.

Claims 1-13 have been canceled.
Claims 14, 15, and 23 have been amended.
Claims 27-32 have been added.
Claims 14-32 are pending in the instant application.
Claims 16-20 and 22 stand withdrawn from consideration as being drawn to a nonelected species while claims 25 and 26 stand withdrawn as being drawn to a nonelected group. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the restriction requirement mailed March 19, 2008.

In the reply filed on April 18, 2008, applicant elected without traverse of the species of anti-PACAP antibodies as a PACAP inhibitor. Newly submitted claims 30 and 31 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: These claims recite using compounds which inhibit the expression of PACAP, with recited species being RNAi and other agents that interfere with the transcription and translation of the PACAP gene. As previously stated, applicant has elected antibodies that bind PACAP as the "agent" to be used in the claimed methods of treating thrombocytopenia, and the mechanism of action whereby antibodies and things like RNAi serve to reduce the effective concentration of PACAP in a patient are distinct, leading to numerous potential differences in things such as administration, efficacy, and side effects.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 30 and 31 withdrawn from consideration

as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 14, 15, 21, 23, 24, 27-29, and 32 are under examination as they read on methods of treating thrombocytopenia by administering the PACAP inhibitor species of antibodies that bind PACAP.

Specification

2. The specification is objected to because page 18 discloses biological sequences not identified by a SEQ ID numbers. It is noted that the sequence listing filed 7/15/05 does appear to disclose these sequences. As such, it appears that the specification needs to be amended to insert the SEQ ID numbers and that submission of a new sequence listing is not required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 14, 15, 21, 24, and 27-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating thrombocytopenia with antibodies that bind PACAP, does not reasonably provide enablement for methods of prevention or methods of treatment with the genus of all inhibitors of PACAP signaling. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons of record.
The office action mailed July 9, 2008 states:

> Applicant has claimed methods of preventing and treating thrombocytopenia by administering inhibitors of PACAP signaling. A working example is provided wherein an antibody that binds the PACAP peptide is administered to mice. Mice receiving the antibody administration

were observed to have circulating platelet levels that were greater than that observed in normal controls, and such mice recovered more quickly from chemically induced thrombocytopenia than normal counterparts. As such, it appears that administering an antibody that binds the PACAP peptide can induce the release of greater than normal levels of platelets from megakaryocytes, and that such a method would be beneficial in treating thrombocytopenic patients who have insufficient levels of platelets to support normal homeostasis. Thus, applicant's method appears to work by increasing platelet titers. Megakaryocyte maturation and platelet release are complex biological phenomena governed by a myriad of factors including cytokines and integrins (Takizawa et al., and Dhanjal et al.). To this field of endeavor, applicant has added PACAP signaling.

PACAP is a peptide that binds to a least 3 distinct receptors (see particularly page 3 of the specification and Table I of Sherwood et al.) One receptor (PACAPR) appears to only bind PACAP, while the other two receptors (VPAC1 and VPAC2) bind PACAP and VIP. VIP is an endogenous peptide that comprises a distinct amino acid sequence as compared to PACAP and is implicated in a wide variety of physiological responses (Sherwood et al., see particularly Figure 3, section A on pages 635-636, and section V beginning on page 639). Note that while both PACAP and VIP have been reported to have an array of diverse functions in the nervous, endocrine, cardiovascular, muscular and immune systems, there are differences in tissue distribution and receptor usage as described previously, and thus VIP and PACAP are not absolutely redundant and interchangeable in all physiological settings. The specification defines "PACAP signaling" as encompassing binding of PACAP to PACAPR, VPAC1, and VPAC2, as well as VIP binding to VPAC1 and VPAC2. Thus it is clear that there are multiple signaling pathways that applicant has aggregated under the term "PACAP signaling". The specification demonstrates that by reducing the level of PACAP peptide by administering an antibody that binds PACAP, a rise in platelet titer can be observed. The specification does not indicate if this effect is due to lack of signaling by PACAPR, VPAC1, VPAC2, or some combination of said receptors. As such, which receptor(s) is/are important for the observed rise in platelet titers? Given that VPAC1 and VPAC2 are not specific for PACAP, signaling through these receptors can still occur via interactions with VIP. Given that multiple pathways are involved in PACAP signaling, it is clear that agents contemplated in the specification as "inhibitors of PACAP" cannot simultaneously block all the pathways. Even in the case of administering antibodies that bind the PACAP peptide, the VIP peptide is still able to interact with VPAC1 and VPAC2 to promote "PACAP signaling". Thus, while it is reasonable that PACAP signaling can be inhibited and thus thrombocytopenia can be treated, it does not appear that PACAP signaling can be completely blocked such that thrombocytopenia can be "prevented". It should be noted that page 10 of the instant specification indicates that "anti-PACAP antibodies" bind PACAP, VIP, or any functional derivative thereof. The specification does not demonstrate that anti-VIP antibodies are able to increase platelet titers, and given the structural, distributional and receptor differences between PACAP and VIP, it does not seem reasonable that antigen specificity can be considered completely interchangeable in the absence of additional data. Also, since the method is performed in a subject, the administered "anti-PACAP antibody" must be able to bind an endogenous peptide, such as PACAP. However, the definition of "anti-PACAP" encompasses antibodies that bind derivatives (such as non-naturally occurring molecules), yet said definition does not indicate that antibodies that bind derivatives must also be able to crossreact with native endogenous peptides. Thus, the full scope of "anti-PACAP" is not reasonably enabled. Further, while the specification discusses the terms "treatment" and "prevention" on page 11 of the instant specification, no guidance is given as to what level of efficacy is required for these terms. Thus, it appears that the term "prevention" encompasses 100% efficacy in 100% of patents, a level of operability that is not reasonably supported by the examples of the instant specification.

Therefore, given the breadth of the claimed invention, the guidance and direction present in the instant specification, the nature of the working examples, and the teachings of the art, a skilled artisan would not be able to practice the breadth of applicant's claimed invention without first conducting additional unpredictable experimentation.

Applicant's arguments filed January 9, 2009 have been fully considered but they are not persuasive. Applicant argues that the claims have been narrowed such that the administered compound must inhibit PACAP production and or activity rather than the previous recitation of "preventing PACAP signaling". This is argued as being narrowing since compounds, such as antibodies that bind VIP, while being disclosed as "PACAP signaling inhibitors" are not reasonably compound that inhibit the production or activity of PACAP itself. Applicant continues this argument by asserting that any method which lowers the effective amount of PACAP will equally result in a beneficial effect on thrombocytopenia.

These arguments have been considered but are not fully persuasive. While applicant is correct that the claims as amended limit the structure of the administered compounds and have removed the limitation of "prevention", they are still not enabled for their full breadth. For example, dependent claim 21 recites that the inhibitory compounds include transdominant receptors. As discussed in the rejection of record, the interactions between peptides and receptors in the PACAP signaling pathway is complex. Indeed, PACAP can be bound by the PACAP receptor as well as VPAC1 and VPAC2. Since all of these bind PACAP, they all presumably would decrease the effective concentration of PACAP. However, use of VPAC1 or VPAC2 would also decrease VIP concentrations. There is no working example of decreasing VIP concentrations in the instant specification, and as such it is not clear how decreasing both PACAP and VIP would impact thrombocytopenia, since VIP and PACAP are not completely redundant and perfectly interchangeable. Further, what is the transdominant receptor? Is it a soluble version of a receptor, or is it a transmembrane molecule that is defective for signaling that would need to be expressed in a cell type of interest, presumably being introduced to a patient via gene therapy with a retroviral construct of some sort? What cell type would need to be targeted? Megakaryocytes? Megakaryocyte precursor cells? Some other cell type that releases soluble mediators that influence the maturation of megakaryocytes into platelets? All of the above? Further, claim 21 also recites "a tertameric peptide". Does this "tetrameric peptide" bind

PACAP, does it bind one of the receptors capable of binding PACAP, or does it do something else entirely?

Also, the claims recite inhibiting PACAP activity. While it is clear than an antibody can bind PACAP and stop PACAP from interacting with its receptors as has been done in the working example disclosed in the instant specification, PACAP has many activities in addition to its role in platelet formation. Indeed, it was first identified in hypothalamus extracts and has been located in the central and peripheral nervous system, the urogenital system, the gastro-intestinal tract, and in several endocrine glands (see page 2 of the instant specification). As such, there appear to be multiple "activities" of PACAP, many of which are unrelated to platelets. Thus, it is not clear that the genus of any and all compounds which inhibit "the production and/or activity" of PACAP potentially anywhere and everywhere within the body would be beneficial or efficacious. It is noted that antibodies have the potential to affect other organ systems and tissues which express PACAP, but the working example does not demonstrate evidence that effects other than boosting platelet numbers were observed. Since much of the breadth of what applicant wishes to use as "inhibiting compounds" work via mechanistic pathways which are quite distinct from antibodies that bind PACAP, it is not reasonable to generalize the results with antibodies to other compounds which comprise different mechanisms of action. Applicant is reminded that "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The “amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." In the instant case, the art does not appear to have identified any role for PACAP in platelet

maturation prior to the filing of the instant application. Further, in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "[W]here there is "no indication that one skilled in [the] art would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects," an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement" and "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis." Given that the only information concerning PACAP involvement in platelet maturation is that which applicant has chosen to disclose in the instant specification, and the fact that many of the compounds recited for use in the claimed methods reduce the effective concentration of PACAP by very different pathways, the demonstration that administration of antibodies that bind PACAP to mice does not validate the hypothesis that any and all methods of inhibiting the effective concentration of PACAP are effective and interchangeable for treating thrombocytopenia. Therefore, the rejection has been maintained.

5. Claims 14, 15, 21, 24, and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for the reason of record. The office action mailed July 9, 2008 states:

> Applicant has claimed broad methods of administering inhibitors of "PACAP signaling". Dependent claim 21 recites a structurally and mechanistically diverse set of molecules that can be used to perform the instant claimed methods, including antisense, RNAi, small molecules, antibodies, and ribozymes without indicating any antigen or target specificity for the recited

molecules. Dependent claim 15 recites that the inhibitor targets expressed PACAP, but recites no structure for the inhibitor itself.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

The instant specification defines "PACAP signaling" on page 9 as involving the binding of two peptides, VIP and PACAP to three distinct receptors (PACAP, VPAC1, and VPAC2). The recited inhibitors of claim 21 are all structurally and therefore mechanistically diverse in their mechanism of action. Thus it is not reasonable to say that they comprise a shared structure that is correlated with the activity of PACAP signaling. Further, what molecule is being targeted by the antisense, RNAi, or antibody of the claim? Even if a target is specified, such as targeting expressed PACAP for example, it does not appear that the specification provides adequate written description to demonstrate that applicant was in possession of the recited genus at the time the application was filed. For example, applicant indicates that small molecule inhibitors can be obtained by screening combinatorial, natural and random peptide libraries (see particularly page 13). As such it is clear that the structure of said small molecules was wholly unknown to applicant at the time the instant invention was filed since such screening assays were not performed and the possible starting materials literally include anything that can be thought of that can be run through a screening assay.

Thus, a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of inhibitors of PACAP signaling inhibitors at the time the instant invention was filed.

Applicant's arguments filed January 9, 2009 have been fully considered but they are not persuasive. Applicant argues that the claims have been narrowed such that they refer to PACAP only, and not to VIP or one of the receptors.

This argument is not persuasive. The amended claims recite "a compound inhibiting PACAP production and/or activity". PACAP is a small peptide that when bound by receptors stimulates cAMP production and inhibits megakaryocyte maturation into platelets. Thus, "activity" can be inhibited by disrupting the binding of PACAP to its receptors. The working example demonstrates the use of antibodies that bind PACAP as one compound suitable fro practicing the instant methods, but others are clearly possible. One such example is the antisense to VPAC1. If the expression of the receptor is inhibited, any signaling of the receptor, and thus at least one activity of the ligand (PACAP) has been inhibited. Thus, the breadth of the claimed invention is not limited to PACAP only, and thus applicant has argued limitations not claimed. The rejection is maintained.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. The rejection of claims 14, 15, 21, 23, and 24 under 35 U.S.C. 102(b) as being anticipated by DiCicco-Bloom et al. (US 2002/0182729A1, of record) has been withdrawn in view of applicant's claim amendments received January 9, 2009.

8. The following are new grounds of rejection necessitated by the claim amendments received January 9, 2009.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites the limitation "said inhibitor". There is insufficient antecedent basis for this limitation in the claim. Note that independent claim 14 has been amended to remove “inhibitor of PACAP signaling” and to add the phrase “a compound inhibiting”. Thus, amendment of the dependent claims to accurately reflect the word usage of the independent claim is suggested.

Claim Objections

11. Claims 23 is objected to as being dependent upon a rejected independent claim, but would be allowable if rewritten in independent form including all of the limitations of the independent claim and any intervening claims. Also, it is suggested that claim 32 be amended to recite “capable of binding to a polypeptide consisting of the amino acid sequence of SEQ ID NO:1”.

12. No claims are allowable.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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